BMC Cancer

RESEARCH Open Access

Association between *NAT10* gene rs8187 G > A polymorphism and Wilms tumor susceptibility in Chinese Han children: a five-center case-control study

Changmi Deng[1†], Jinhong Zhu[2†], Fei Duan[3†], Wenli Zhang[1], Haixia Zhou[4], Suhong Li[5], Jiao Zhang[6], Jiwen Cheng[7], Wen Fu[1], Jing He[1], Huizhong Niu[3*] and Rui-Xi Hua[1*]

Abstract

Background Wilms tumor, a prevalent pediatric kidney cancer, has been extensively studied to elucidate its genetic mechanisms. *NAT10* (*N-acetyltransferase 10*) is a gene encoding acetyltransferase, which is involved in various cellular processes, including RNA modification, DNA repair, and protein acetylation. The oncogenic role of NAT10 in cancer has garnered significant attention. However, research on *NAT10* genetic variants and their associations with cancer is nascent.

Methods This study investigated the link between *NAT10* genetic variants and Wilms tumor risk via a case–control design with genomic DNA from 414 patients and 1199 controls. Genotyping was performed via the TaqMan method, and logistic regression statistical analysis was conducted to identify significant associations, followed by extra analysis to minimize false positive significant results.

Results Our findings revealed that the rs8187 G > A polymorphism in the *NAT10* gene is significantly correlated with a decreased risk of developing Wilms tumor (GA vs. GG, adjusted odds ratio (AOR) = 0.60, 95% confidence interval (CI) = 0.46–0.77, $P < 0.0001$; GA/AA vs. GG, AOR = 0.74, 95% CI = 0.59–0.93, $P = 0.011$). Stratified analyses further revealed a significant association in children aged 18 months or under and in subgroups with stage II, stage IV, or combined stage I + II tumors.

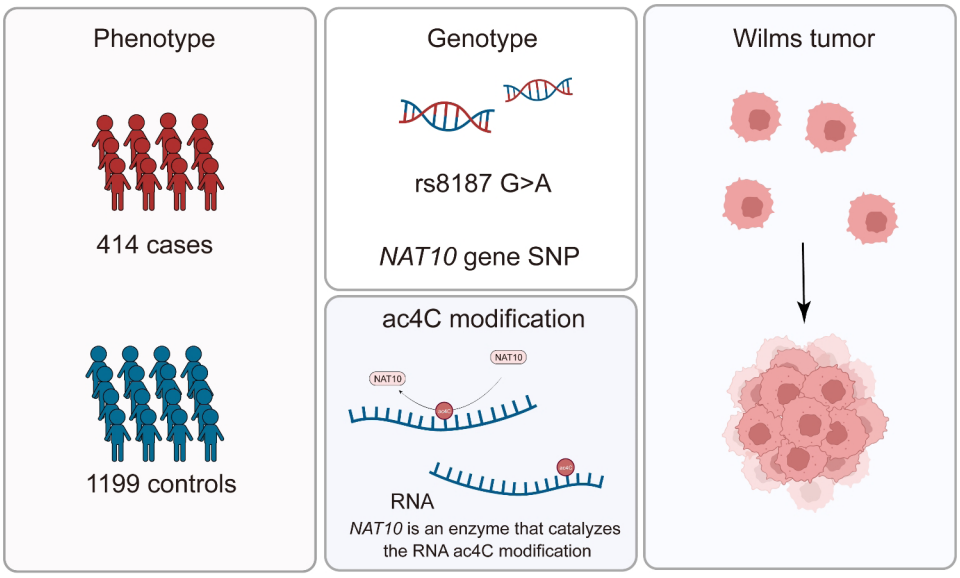
Conclusion These results highlight the potential of *NAT10* rs8187 G > A polymorphism as genetic markers for Wilms tumor susceptibility. This study clarifies the genetic basis of Wilms tumor susceptibility and highlights the role of *NAT10* rs8187 G > A polymorphism in early detection and risk assessment.

†Changmi Deng, Jinhong Zhu and Fei Duan contributed equally to this work.

*Correspondence:
Huizhong Niu
nrlnhz@163.com
Rui-Xi Hua
huaruix@mail.sysu.edu.cn

Full list of author information is available at the end of the article

Graphical Abstract



Associaiton of *NAT10* gene rs8187 G>A polymorphism with Wilms tumor risk

Keywords Wilms tumor, Susceptibility, *NAT10*, rs8187, Polymorphism

Introduction

Wilms tumor, or nephroblastoma, is the most prevalent pediatric renal malignancy. The condition affects approximately 1 in 10,000 children, with prevalence dynamics peaking at 3 years of age [1]. Wilms tumor is an embryonal tumor in children, exemplifying the connection between disrupted organ development and tumor formation. It arises from primitive renal cells that fail to differentiate properly during early nephrogenesis, instead leading to the development of malignancy. The typical clinical presentations of Wilms tumor include an abdominal mass, hematuria, hypertension, abdominal pain, fever, and Malaise [2]. Advancements in treatment have led to a significantly improved prognosis in children with Wilms tumor, with a 5-year survival rate of over 90% for children with in situ disease [3]. However, early detection and comprehensive care are crucial for optimizing outcomes and minimizing long-term complications.

The environmental causative factors for Wilms tumor remain unclarified [3]. Genetic variations are crucial in Wilms tumor development. First, Wilms tumor is associated with mutations in approximately 40 different genes, such as *CTNNB1*, *DROSHA*, *WT1*, *MYCN*, *TP53*, and *SIX1* [3]. The molecular drivers frequently impede genetic pathways crucial for normal embryogenesis of the genitourinary tract but are not confined to these pathways [3]. Second, certain genetic syndromes are associated with a greater risk of developing Wilms tumor, such as aniridia, genitourinary anomalies, and mental retardation syndrome, Beckwith–Wiedemann syndrome, and Denys–Drash syndrome [3]. Additionally, single nucleotide polymorphisms (SNPs) are the most common type of genetic variation among individuals and contribute to genetic diversity within a population. They are a major source of genetic variation that underpins individual differences in cancer susceptibility [4, 5]. Many studies have been performed to discover Wilms tumor susceptibility polymorphisms via candidate gene strategies [6–14] or genome-wide association studies (GWASs) [15]. As a result, SNPs in many important genes, such as *MTHFR* [14] and *RECK* [11], as well as genes in the 5q14, 22q12, and Xp22 regions [15], have been demonstrated to modulate Wilms tumor predisposition. Despite significant advances in Wilms tumor cancer biology, the genetic and molecular underpinnings of Wilms tumor remain incompletely understood.

The N-acetyltransferase 10 protein, encoded by the *NAT10* gene, is a member of the GCN5-related N-acetyltransferase family. NAT10 is responsible for transferring acetyl-CoA donor acetyl groups to an amino group or an RNA cytidine, contributing to ribosome biogenesis, translation efficiency, cell division, cell metabolism, telomere maintenance and aging [16]. NAT10 is an essential gene at both the organism and the cellular level [16], as demonstrated by the fatality of the deletion of both NAT10 alleles in mouse embryos [17] and

the failure to create NAT10 knockout cell lines [18]. In contrast, NAT10 overexpression enhances tumor development, and its protein and mRNA levels are markedly higher in cancerous tissues than in normal tissues [16, 19, 20]. Studies are increasingly pointing to NAT10 as an oncogene and a druggable target in a broad spectrum of cancers [16], such as hepatocellular carcinoma [21, 22], laryngeal squamous cell carcinoma [23], lung adenocarcinoma [24], colorectal carcinoma [25], acute myeloid leukemia [26], breast cancer [27], gastric cancer [28], and bladder cancer [29]. Given these observations, potential functional polymorphisms in the *NAT10* gene that affect gene function may disrupt cellular homeostasis and thereby contribute to interindividual differences in cancer susceptibility. However, there is no published evidence of the relationship between *NAT10* gene polymorphisms and cancer susceptibility. SNPs are the most common type of genetic variation and have been implicated in numerous diseases, including various forms of cancer. Thus, we selected *NAT10* as a candidate gene for this investigation.

This study aimed to investigate the potential correlation between *NAT10* gene SNPs and Wilms tumor, addressing a critical gap in the current understanding of the genetic factors contributing to this pediatric malignancy. By elucidating this relationship, we hope to provide insights that could lead to improved diagnostic and therapeutic strategies for Wilms tumor.

Methods and materials

Study population

In this study, 414 offspring of Han Chinese heritage with histologically confirmed Wilms tumor were recruited, along with 1199 age- and sex-matched healthy controls, as we described previously (Table S1) [30, 31]. The Wilms tumor diagnosis was based on clinical evaluation, imaging studies, and histological confirmation, following established diagnostic criteria. The study followed the Declaration of Helsinki guidelines and was approved by the Ethics Committee of Guangzhou Women and Children Medical Center (No. 202016601). Informed consent was signed by the parents or legal guardians of all the participants. Prior to any medical procedures, venous blood samples were collected from each participant to ensure the accuracy and reliability of the study data.

SNP selection

The selection of candidate SNPs in the *NAT10* gene was initially carried out via the dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP), following the criteria outlined in prior studies [32]. By considering the SNP location, minor allele frequency in the Chinese Han population, potential functions, and low linkage disequilibrium (LD), only one eligible SNP, *NAT10* rs8187 (G > A), was identified. A silico tool, SNPinfo (https://snpinfo.niehs.nih.gov), predicts that this SNP may potentially lead to disruption in microRNA-binding sites, suggesting a post-transcriptional regulatory mechanism.

TaqMan genotyping assay with validation and quality control

DNA extraction from peripheral blood samples was carried out via Tiangen Blood DNA Extraction kits (Tiangen Biotechnology, Beijing, China). Afterward, the DNA concentration of each sample was assessed with a spectrophotometer and adjusted to achieve the required concentration. SNP genotyping was conducted via TaqMan real-time PCR on a TaqMan instrument (Applied Biosystems, Foster City, CA) [33–35]. The quality control measures included negative controls without DNA templates on each 384-well plate to monitor contamination and positive controls with predetermined genotypes to confirm assay accuracy. Each plate included at least four positive controls representing different genotypes, such as wild type, homozygous, and heterozygous. Technical replicates were used on each plate to evaluate reproducibility, and 5–10% of the samples were subjected to repeat genotyping across plates to ensure > 99% agreement. The error rate was determined by cross-referencing initial and repeated genotyping results, and no discrepancies were observed, confirming a 0% error rate.

False-positive report probability analysis

The false-positive report probability (FPRP) is a statistical metric used to determine the chance of a positive finding reported in a study being a false positive. FPRP analysis comprehensively considers statistical significance (*P* value), statistical power, and the prior probability of the hypothesis. Prior probability is the probability given to a hypothesis prior to evaluating current evidence, which represents the initial belief about the hypothesis's validity on the basis of existing knowledge, background information, or historical data. Since the association study involved multiple tests, we performed an FPRP analysis to examine whether the significant results were false positives or deserved attention. The moderate (e.g., 0.1 to 0.5) and low (e.g., below 0.1) thresholds of prior probability were chosen for this study. Given the exploratory nature of this study and the relatively moderate sample size, we adopted an FPRP threshold of 0.20 to balance the risk of false positives with the need to identify potentially meaningful associations for future validation.

Statistical analysis

A chi-square goodness-of-fit test was adopted to evaluate the consistency of the genotype frequency distribution of the *NAT10* rs8187 G > A polymorphism with Hardy-Weinberg equilibrium (HWE) exclusively in the control

group. A *P*-value > 0.05 was considered consistent with HWE, indicating that genotype distributions were representative of the general population. We then used logistic regression analysis to assess the relationship between the *NAT10* rs8187 G > A polymorphism and susceptibility to Wilms tumor. The odds ratio (OR) and 95% confidence interval (CI) were calculated across various genetic models, such as homozygous (AA vs. GG), heterozygous (GA vs. GG), dominant (GA/AA vs. GG), recessive (AA vs. GA/GG), and additive based on standard epidemiological approaches for genetic association studies. Briefly, the dominant Model (GA/AA vs. GG) assumes that carrying at least one minor allele (A) may confer risk, reflecting a potential dominant effect of the polymorphism. The recessive Model (AA vs. GA/GG) evaluates whether two copies of the minor allele (A) are required to influence susceptibility, indicative of a recessive effect. The additive model (0, 1, or 2 copies of A allele) tests for a dose-dependent relationship between the number of minor alleles and disease risk, offering sensitivity to detect linear trends in genetic effects. The use of multiple genetic models allows us to comprehensively investigate different inheritance patterns, enhancing our ability to capture the true genetic mechanism underlying disease susceptibility. All models were adjusted for age, sex, and clinical stage. Statistical evaluations were carried out via SAS v9.4 (SAS Institute Inc., Cary, NC), with the significance level set at a *P* value of less than 0.05 (two-sided).

Results

Association results

A total of 414 Wilms tumor cases and 1199 controls were initially enrolled in the study. However, 23 cases were excluded due to insufficient DNA quality or quantity. Genotyping of the *NAT10* rs8187 G > A polymorphism was successfully performed in 391 cases and 1199 controls. Prior to association analysis, we determined that the genotype frequency distribution of the *NAT10* rs8187 G > A polymorphism aligns with HWE in the control subjects ($P = 0.803$). Table 1 presents the association results between the *NAT10* rs8187 polymorphism and the risk of Wilms tumor. Specifically, the GA genotype (adjusted OR (AOR) = 0.60, 95% CI = 0.46–0.77) demonstrated a 40% reduction in Wilms tumor risk, suggesting a potentially protective effect associated with the rs8187 polymorphism. The narrow CI observed (0.46–0.77) suggests a robust association unlikely to result from random variation, further supporting the significance of the findings. In the dominant genetic model, compared with the GG genotype, the combined GA and AA genotypes of the *NAT10* rs8187 polymorphism were significantly associated with a reduced risk of developing Wilms tumor (AOR = 0.74, 95% CI = 0.59–0.93, $P = 0.011$). Importantly, when the recessive genetic model was assumed, the homozygotes of the SNP exhibited increased susceptibility to Wilms tumor (AA vs. GG/GA) (AOR = 1.50, 95% CI = 1.13–1.99, $P = 0.005$).

Stratified analyses (Table 2) were performed by age, sex, and clinical stage with the application of the dominant genetic model (GA/AA vs.GG). When the cohort was stratified by age, we observed significant associations in the subgroups aged 18 months or younger (adjusted OR = 0.63, 95% CI = 0.43–0.93; $P = 0.019$) [GA /AA (case/control: 76/156) vs. GG (case/control: 61/156)]. Furthermore, stratification by clinical stage revealed significant results in subgroups with stage II (adjusted OR = 0.59, 95% CI = 0.40–0.88, $P = 0.009$) [GA /AA (case/control: 58/768) vs. GG (case/control: 54/430)], stage IV (adjusted OR = 0.54, 95% CI = 0.30–0.98, $P = 0.042$) [GA /AA (case/control: 137/768) vs. GG (case/control: 103/430)], and combined stage I + II (adjusted OR = 0.73, 95% CI = 0.55–0.97, $P = 0.028$) [GA /AA (case/control: 137/768) vs. GG (case/control: 103/430)] tumors.

FPRP analysis results

When the prior probability of 0.25 was assumed, i.e., an initial 25% belief that the hypothesis is true, all the significant results were significantly noteworthy with the

Table 1 Association between *NAT10* gene rs8187 G > A polymorphism and Wilms tumor risk

Genotype	Cases (*N* = 391)	Controls (*N* = 1198)	*P*[a]	Adjusted OR (95% CI) [b]	*P*[b]
	No. (%)	No. (%)			
rs8187 (HWE = 0.803)					
GG	168 (42.97)	430 (35.89)		1.00	
GA	134 (34.27)	572 (47.75)		**0.60 (0.46–0.77)**	**< 0.0001**
AA	89 (22.76)	196 (16.36)		1.15 (0.85–1.57)	0.371
Additive			0.873	0.98 (0.84–1.15)	0.826
Dominant (GA/AA)	223 (57.03)	768 (64.11)	0.012	**0.74 (0.59–0.93)**	**0.011**
GG/GA	302 (77.24)	1002 (83.64)		1.00	
AA	89 (22.76)	196 (16.36)	0.004	**1.50 (1.13–1.99)**	**0.005**

OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium

[a] χ^2 test for genotype distributions between Wilms tumor patients and cancer-free controls

[b] Adjusted for age and gender

Table 2 Stratify analysis of *NAT10* gene rs8187 G > A polymorphism with Wilms tumor risk

Variables	GG	GA/AA	Adjusted OR [a]	*P*[a]
	No. of case/control	No. of case/control	(95% CI)	
Age, month				
≤ 18	61/156	76/309	**0.63 (0.43–0.93)**	**0.019**
> 18	107/274	147/459	0.81 (0.61–1.09)	0.161
Gender				
Females	78/182	106/339	0.73 (0.52–1.03)	0.071
Males	90/248	117/429	0.75 (0.55–1.02)	0.070
Clinical stages				
I	49/430	79/768	0.87 (0.60–1.27)	0.478
II	54/430	58/768	**0.59 (0.40–0.88)**	**0.009**
III	33/430	56/768	0.97 (0.62–1.52)	0.900
IV	23/430	22/768	**0.54 (0.30–0.98)**	**0.042**
I + II	103/430	137/768	**0.73 (0.55–0.97)**	**0.028**
III + IV	56/430	78/768	0.79 (0.55–1.14)	0.215

OR, odds ratio; CI, confidence interval

[a] Adjusted for age and gender, omitting the corresponding variable

Table 3 False-positive report probability analysis for the significant finding between *NAT10* gene rs8187 G > A polymorphism and Wilms tumor risk

Genotype	OR (95% CI)	*P*[a]	Statistical power [b]	Prior probability				
				0.25	0.1	0.01	0.001	0.0001
GA vs. GG	0.60 (0.46–0.78)	0.0001	0.298	**0.001**	**0.003**	**0.032**	0.251	0.770
AA vs. GA/GG	1.51 (1.14-2.00)	0.004	0.491	**0.026**	**0.073**	0.464	0.897	0.989
GA/AA vs. GG	0.74 (0.59–0.94)	0.012	0.812	**0.043**	**0.120**	0.600	0.938	0.993
≤18 months	0.63 (0.43–0.93)	0.019	0.378	**0.132**	0.314	0.834	0.981	0.998
II	0.60 (0.41–0.89)	0.010	0.300	**0.094**	0.238	0.774	0.972	0.997
IV	0.54 (0.30–0.97)	0.040	0.239	0.335	0.601	0.943	0.994	0.999
I + II	0.75 (0.56–0.99)	0.040	0.772	**0.135**	0.319	0.838	0.981	0.998

OR, odds ratio; CI, confidence interval

[a] Chi-square test was used to calculate the genotype frequency distributions

[b] Statistical power was calculated using the number of observations in each subgroup and the corresponding ORs and *P* values in this table

FPRP values less than 0.2, except for the association in the tumor-stage IV group (Table 3). Next, we set the prior probability as 0.1, indicating a lower chance of a false positive due to a firmer initial belief in the hypothesis. We found that the overall association between the *NAT10* rs8187 G > A polymorphism and Wilms tumor susceptibility remains significant for the heterozygous (GA vs. GG), recessive (AA vs. GA/GG), and dominant (GA/AA vs. GG) models. Even when a low prior probability of 0.01 was adopted, the association under the heterozygous model remained statistically credible. These results strongly confirmed that the reported positive association between the *NAT10* rs8187 G > A polymorphism and Wilms tumor susceptibility remains significant even under conservative prior probabilities, thus minimizing the risk of false positives (Table 3).

Discussion

The current study established a link between a *NAT10* gene variant and Wilms tumor susceptibility. Specifically, individuals with only the GA genotype or those with the combined GA and AA genotypes of the *NAT10* rs8187 G > A polymorphism were at a reduced risk of developing Wilms tumor compared with those with the GG genotype. The stratified analysis highlighted significant associations in children 18 months or younger and in subgroups with stage II, IV, and I + II tumors. In addition, our FPRP analysis indicates the robustness of the significant associations reported in this study. The relatively low FPRP values suggest that the *NAT10* rs8187 G > A polymorphism may play a biologically relevant role in Wilms tumor susceptibility. However, FPRP values are dependent on prior assumptions, and further validation studies in larger populations are recommended to confirm our results.

Our results are comparable to findings from other studies investigating genetic factors in Wilms tumor. For example, similar studies have explored the role of various gene polymorphisms in Wilms tumor [10–13]. For example, in Chinese children, a significant correlation was found between the G allele of rs11788747 in the *RECK* gene and Wilms tumor [11]. In contrast, a case–control

study indicated that male carriers of the G allele of the *FOXP3* rs2232365 polymorphism had a reduced risk of Wilms tumor [10]. Importantly, throughout the past ten years, our research team has pinpointed Wilms tumor susceptibility SNPs in multiple genes by applying the candidate gene approach in a cohort of 414 Wilms tumor patients and matched healthy controls. These Wilms tumor predisposition genes include oncogenes [6–8], tumor suppressors [36], genes related to fundamental cellular processes such as DNA repair [37, 38], RNA m^6A modification [39–41], and RNA m^7G modification [42, 43]. These findings support a genetic predisposition to the disease.

NAT10 acts as a lysine acetyltransferase, modifying histones and nonhistone proteins [27, 28, 44]. Moreover, it is also responsible for depositing N4-acetylcytidine (ac4C) in RNAs to regulate their stability, translation, and functions [16, 18, 22, 25]. NAT10 is involved in regulating gene expression, DNA repair, and cellular proliferation—all critical factors in cancer development. Functional variants of the *NAT10* gene could impact these cellular processes by altering the acetylation status of proteins or RNA involved in key signaling pathways and effectors, such as those regulating cell cycle progression and apoptosis [20, 45]. In other words, *NAT10* variants have the potential to disrupt these processes, thus leading to uncontrolled cell growth and tumor formation. Specifically, the role of NAT10 in modifying histones and other proteins [27, 28, 44] could influence the chromatin structure and gene expression patterns associated with Wilms tumor pathogenesis. Therefore, it is biologically plausible that changes in *NAT10* activity could lead to dysregulation of these pathways, modulating susceptibility to tumors [45, 46]. The Bioinformatics tools SNPinfo predict that rs8187 G > A polymorphism may possibly regulate *NAT10* gene expression in a post-transcriptional regulatory mechanism by interfering with its microRNA-binding sites. A 40% risk reduction suggests that such variations could affect *NAT10* gene expression, thereby altering NAT10-mediated RNA acetylation patterns and leading to downstream impacts on RNA modification and stability. This could impair pathways critical for uncontrolled cell growth or enhance cellular responses to DNA damage, thereby lowering Wilms tumor susceptibility. Understanding these mechanisms can provide insights into how *NAT10* variants influence tumor risk and identify potential targets for therapeutic intervention.

By establishing a connection between *NAT10* rs8187 G > A polymorphism and Wilms tumor, this study could contribute to the identification of new biomarkers for early detection or risk assessment. *NAT10* gene rs8187 G > A polymorphism strongly associated with Wilms tumor predisposition could be incorporated into genetic screening programs. Early detection through genetic screening could improve survival rates and reduce the overall burden of the disease. In addition, these genetic markers may help stratify patients on the basis of their risk levels, enabling more targeted surveillance and preventive measures. However, while our study supports the potential role of *NAT10* rs8187 as a susceptibility marker, its clinical translation requires further investigation to address challenges related to predictive accuracy, diagnostic specificity population variability, and functional validation. Prospective studies assessing longitudinal risk prediction and integrating machine learning models may help refine the clinical utility of SNP-based biomarkers, including *NAT10* rs8187. Importantly, multi-center collaborations are essential to establish standardized protocols for SNP testing and validation. This research may provide new insights into the genetic factors underlying Wilms tumor susceptibility, particularly focusing on the *NAT10* gene, which has not been extensively studied in this context. This research sets the stage for further studies to explore the functional role of *NAT10* in tumor biology and its interaction with other genetic and environmental factors. These findings can inspire additional research into the role of *NAT10* in other types of cancers.

The limitations of this study may involve, though not be confined to, the following concerns. First, the study's sample size might be limited, affecting the power of the statistical analyses and the precision of the risk estimate. Due to relatively small subgroup sample sizes, stratified analyses may suffer from potential overfitting or reduced statistical power. Second, the study may suffer from selection bias. The participants were recruited from different geographic regions of China. Therefore, the representativity of the broader population of the cohort warrants validation from additional association studies. Third, our finding may have population specificity, and generalizability may be an issue. The findings from the study might not hold true for different age groups, ethnicities, or geographic locations. Replication studies are warranted in diverse ethnic cohorts. Fourth, we adjusted for age and gender in the logistic regression models as they are established demographic confounders in cancer susceptibility studies and influence Wilms tumor risk. However, factors like environmental exposures, socioeconomic status, diet, and family cancer history that may also contribute to susceptibility were not adjusted because these variables were unavailable due to retrospective data collection constraints. Future prospective studies should include detailed data on these variables to assess their influence. Finally, only one SNP was studied, and data concerning environmental factors were missing. Therefore, our results should be interpreted with caution. Future research may involve investigating the mechanisms underlying the observed associations or

conducting multicenter, large-scale studies to confirm and expand upon the current findings.

Conclusion

In conclusion, this study revealed a significant association between the *NAT10* gene rs8187 G > A polymorphism and Wilms tumor susceptibility in the Chinese Han Children, particularly between the combined GA and AA genotypes of the *NAT10* rs8187 polymorphism and reduced Wilms tumor risk. Replication studies should be conducted in ethnically diverse cohorts to validate the findings. Overall, this study contributes to the understanding of genetic factors involved in Wilms tumor susceptibility by introducing a new genetic player, with potential implications for early detection, risk assessment, and personalized treatment strategies.

Abbreviations

SNP	Single nucleotide polymorphism
GWAS	Genome-wide association study
LD	Linkage disequilibrium
FPRP	False-positive report probability
HWE	Hardy–weinberg equilibrium
OR	Odds ratio
CI	Confidence interval
ac4C	N4-acetylcytidine

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-025-13922-6.

Supplementary Material 1

Acknowledgements

Not applicable.

Author contributions

All the authors contributed significantly to this work. JH, HN, and RXH designed the research study; HZ, SL, JZhang, JC, WF, and JH performed the research study and collected the samples and clinical data; WZ and JH analyzed the data and prepared the Tables; CD, JZhu, FD, HN, and RXH wrote the paper. All the authors have read and approved the final version of the manuscript.

Funding

This study was funded by grants from the Youth Medical Innovation and Practice Research Program of Guangzhou (No: 2023QNYXYB010), the National Natural Science Foundation of China (No: 82003523), Guangzhou Science and Technology Project (No: 2025A03J4476, 2025A04J4697), and the Major Science and Technology Special Project of Wenzhou (No: ZY2020021).

Data availability

All the data are available upon request from the corresponding authors.

Declarations

Ethics approval and consent to participate

The study followed the Declaration of Helsinki guidelines and was approved by the Ethics Committee of Guangzhou Women and Children Medical Center (No. 202016601). Informed consent was signed by the parents or legal guardians of all the participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Novelty Statements

This is the first Wilms tumor-specific study on *NAT10* gene rs8187 G > A polymorphism. In this five-center case-control study with 414 Wilms tumor cases and 1199 controls, we found that *NAT10* gene rs8187 G > A polymorphism is significantly correlated with a decreased risk of developing Wilms tumor, which is more prominent in children aged 18 months or under and in subgroups with stage II, stage IV, or combined stage I + II tumors.

Author details

[1]Department of Pediatric Surgery, Guangzhou Institute of Pediatrics, Guangdong Provincial Key Laboratory of Research in Structural Birth Defect Disease, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, 9 Jinsui Road, Guangzhou 510623, Guangdong, China
[2]Department of Clinical Laboratory, Biobank, Harbin Medical University Cancer Hospital, Harbin 150040, Heilongjiang, China
[3]Department of Pediatric General Surgery, Hebei Children's Hospital of Hebei Medical University, No. 133 of Jianhua South Street, Yuhua District, Shijiazhuang 050031, Hebei, China
[4]Department of Hematology, The Key Laboratory of Pediatric Hematology and Oncology Diseases of Wenzhou, The Second Affiliated Hospital, Yuying Children's Hospital of Wenzhou Medical University, Wenzhou 325027, Zhejiang, China
[5]Department of Pathology, Children Hospital and Women Health Center of Shanxi, Taiyuan 030013, Shannxi, China
[6]Department of Pediatric Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan 450052, China
[7]Department of Pediatric Surgery, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710004, Shaanxi, China

Received: 3 December 2024 / Accepted: 12 March 2025
Published online: 17 March 2025

References

1. Perotti D, Williams RD, Wegert J, Brzezinski J, Maschietto M, Ciceri S, Gisselsson D, Gadd S, Walz AL, Furtwaengler R, et al. Hallmark discoveries in the biology of Wilms tumour. Nat Rev Urol. 2024;21(3):158–80.
2. Welter N, Brzezinski J, Treece A, Chintagumpala M, Young MD, Perotti D, Kieran K, Jongmans MCJ, Murphy AJ. The pathophysiology of bilateral and multifocal Wilms tumors: what we can learn from the study of predisposition syndromes. Pediatr Blood Cancer. 2023;70(Suppl 2):e29984.
3. Spreafico F, Fernandez CV, Brok J, Nakata K, Vujanic G, Geller JI, Gessler M, Maschietto M, Behjati S, Polanco A, et al. Wilms tumour. Nat Rev Dis Primers. 2021;7(1):75.
4. Houlston RS, Peto J. The search for low-penetrance cancer susceptibility alleles. Oncogene. 2004;23(38):6471–6.
5. Imyanitov EN, Togo AV, Hanson KP. Searching for cancer-associated gene polymorphisms: promises and Obstacles. Cancer Lett. 2004;204(1):3–14.
6. Huang X, Zhao J, Zhu J, Chen S, Fu W, Tian X, Lou S, Ruan J, He J, Zhou H. MYCN gene polymorphisms and Wilms tumor susceptibility in Chinese children. J Clin Lab Anal. 2019;33(9):e22988.
7. Fu W, Zhuo Z, Hua RX, Fu K, Jia W, Zhu J, Zhang J, Cheng J, Zhou H, Xia H, et al. Association of KRAS and NRAS gene polymorphisms with Wilms tumor risk: a four-center case-control study. Aging. 2019;11(5):1551–63.
8. Huang X, Zhao J, Fu W, Zhu J, Lou S, Tian X, Chen S, Ruan J, He J, Zhou H. The association of RAN and RANBP2 gene polymerphisms with Wilms tumor risk in Chinese children. J Cancer. 2020;11(4):804–9.
9. Ishibashi CM, de Oliveira CEC, Guembarovski RL, Hirata BKB, Vitiello GAF, Guembarovski AL, Amarante MK, de Oliveira KB, Kishima MO, Ariza CB, et al. Genetic polymorphisms of the TGFB1 signal peptide and promoter region: role in Wilms tumor susceptibility?? J Kidney Cancer VHL. 2021;8(4):22–31.
10. Ozawa PM, Ariza CB, Losi-Guembarovski R, Guembarovski AL, de Oliveira CE, Banin-Hirata BK, Kishima MO, Petenuci DL, Watanabe MA. Wilms' tumor

susceptibility: possible involvement of FOXP3 and CXCL12 genes. Mol Cell Pediatr. 2016;3(1):36.
11. Yu Y, Hu Y, Li K, Chen Z, Zhang H, Zhang L. RECK gene polymorphism is associated with susceptibility and prognosis of Wilms' tumor in Chinese children. Med Sci Monit. 2015;21:1928–33.
12. Vasconcelos GM, Goncalves BA, Montalvao-de-Azevedo R, Thuler LC, Braga FH, Pombo-de-Oliveira MS, de Camargo B. Brazilian embryonal tumor G: PON1 Q192R polymorphism (rs662) is associated with childhood embryonal tumors. Mol Biol Rep. 2014;41(9):6111–5.
13. Radojevic-Skodric S, Basta-Jovanovic G, Brasanac D, Nikolic N, Bogdanovic L, Milicic B, Milasin J. Survivin gene promoter – 31 G/C polymorphism is associated with Wilms tumor susceptibility in Serbian children. J Pediatr Hematol Oncol. 2012;34(8):e310–314.
14. Ferrara M, Capozzi L, Russo R. Impact of the MTHFR C677T polymorphism on risk of Wilms tumor: case-control study. J Pediatr Hematol Oncol. 2009;31(4):256–8.
15. Turnbull C, Perdeaux ER, Pernet D, Naranjo A, Renwick A, Seal S, Munoz-Xicola RM, Hanks S, Slade I, Zachariou A, et al. A genome-wide association study identifies susceptibility loci for Wilms tumor. Nat Genet. 2012;44(6):681–4.
16. Dalhat MH, Narayan S, Serio H, Arango D. Dissecting the oncogenic properties of essential RNA-modifying enzymes: a focus on NAT10. Oncogene. 2024;43(15):1077–86.
17. Balmus G, Larrieu D, Barros AC, Collins C, Abrudan M, Demir M, Geisler NJ, Lelliott CJ, White JK, Karp NA, et al. Targeting of NAT10 enhances healthspan in a mouse model of human accelerated aging syndrome. Nat Commun. 2018;9(1):1700.
18. Liu R, Wubulikasimu Z, Cai R, Meng F, Cui Q, Zhou Y, Li Y. NAT10-mediated N4-acetylcytidine mRNA modification regulates self-renewal in human embryonic stem cells. Nucleic Acids Res. 2023;51(16):8514–31.
19. Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A, Sivertsson A, Kampf C, Sjostedt E, Asplund A et al. Proteomics. Tissue-based map of the human proteome. *Science* 2015, 347(6220):1260419.
20. Yang C, Wu T, Zhang J, Liu J, Zhao K, Sun W, Zhou X, Kong X, Shi J. Prognostic and immunological role of mRNA ac4C regulator NAT10 in Pan-Cancer: new territory for cancer research?? Front Oncol. 2021;11:630417.
21. Tschida BR, Temiz NA, Kuka TP, Lee LA, Riordan JD, Tierrablanca CA, Hullsiek R, Wagner S, Hudson WA, Linden MA, et al. Sleeping beauty insertional mutagenesis in mice identifies drivers of Steatosis-Associated hepatic tumors. Cancer Res. 2017;77(23):6576–88.
22. Pan Z, Bao Y, Hu M, Zhu Y, Tan C, Fan L, Yu H, Wang A, Cui J, Sun G. Role of NAT10-mediated ac4C-modified HSP90AA1 RNA acetylation in ER stress-mediated metastasis and lenvatinib resistance in hepatocellular carcinoma. Cell Death Discov. 2023;9(1):56.
23. Li Z, Li D, Yang T, Yao C. NAT10 promotes the tumorigenesis and progression of laryngeal squamous cell carcinoma through ac4C modification of FOXM1 mRNA. Cancer Biol Ther. 2023;24(1):2274143.
24. Shang X, Peng Y, Wang Y, Feng Z, Li M, Peng Z, Ren W. Profile analysis of N4-acetylcytidine (ac4C) on mRNA of human lung adenocarcinoma and paired adjacent non-tumor tissues. Biochim Biophys Acta Gen Subj. 2023;1867(12):130498.
25. Zheng X, Wang Q, Zhou Y, Zhang D, Geng Y, Hu W, Wu C, Shi Y, Jiang J. N-acetyltransferase 10 promotes colon cancer progression by inhibiting ferroptosis through N4-acetylation and stabilization of ferroptosis suppressor protein 1 (FSP1) mRNA. Cancer Commun (Lond). 2022;42(12):1347–66.
26. Zi J, Han Q, Gu S, McGrath M, Kane S, Song C, Ge Z. Targeting NAT10 induces apoptosis associated with enhancing Endoplasmic reticulum stress in acute myeloid leukemia cells. Front Oncol. 2020;10:598107.
27. Liu HY, Liu YY, Yang F, Zhang L, Zhang FL, Hu X, Shao ZM, Li DQ. Acetylation of MORC2 by NAT10 regulates cell-cycle checkpoint control and resistance to DNA-damaging chemotherapy and radiotherapy in breast cancer. Nucleic Acids Res. 2020;48(7):3638–56.
28. Zhang Y, Jing Y, Wang Y, Tang J, Zhu X, Jin WL, Wang Y, Yuan W, Li X, Li X. NAT10 promotes gastric cancer metastasis via N4-acetylated COL5A1. Signal Transduct Target Ther. 2021;6(1):173.
29. Wang G, Zhang M, Zhang Y, Xie Y, Zou J, Zhong J, Zheng Z, Zhou X, Zheng Y, Chen B, et al. NAT10-mediated mRNA N4-acetylcytidine modification promotes bladder cancer progression. Clin Transl Med. 2022;12(5):e738.
30. Hua RX, Liu J, Fu W, Zhu J, Zhang J, Cheng J, Li S, Zhou H, Xia H, He J, et al. ALKBH5 gene polymorphisms and Wilms tumor risk in Chinese children: A five-center case-control study. J Clin Lab Anal. 2020;34(6):e23251.
31. Hua RX, Fu W, Lin A, Zhou H, Cheng J, Zhang J, Li S, Liu G, Xia H, Zhuo Z, et al. Role of FTO gene polymorphisms in Wilms tumor predisposition: A five-center case-control study. J Gene Med. 2021;23(8):e3348.
32. He J, Wang F, Zhu J, Zhang R, Yang T, Zou Y, Xia H. Association of potentially functional variants in the XPG gene with neuroblastoma risk in a Chinese population. J Cell Mol Med. 2016;20(8):1481–90.
33. Chen YP, Liao YX, Zhuo ZJ, Yuan L, Lin HR, Miao L, Li X, Huang XK, Zhou JY, Bian J, et al. Association between genetic polymorphisms of base excision repair pathway and glioma susceptibility in Chinese children. World J Pediatr. 2022;18(9):632–5.
34. Guan Q, Lin H, Hua W, Lin L, Liu J, Deng L, Zhang J, Cheng J, Yang Z, Li Y, et al. Variant rs8400 enhances ALKBH5 expression through disrupting miR-186 binding and promotes neuroblastoma progression. Chin J Cancer Res. 2023;35(2):140–62.
35. Guan Q, Zhang X, Liu J, Zhou C, Zhu J, Wu H, Zhuo Z, He J. ALKBH5 gene polymorphisms and risk of neuroblastoma in Chinese children from Jiangsu Province. Cancer Innov. 2024;3(2):e103.
36. Fu W, Zhuo ZJ, Jia W, Zhu J, Zhu SB, Lin ZF, Wang FH, Xia H, He J, Liu GC. Association between TP53 gene Arg72Pro polymorphism and Wilms' tumor risk in a Chinese population. Onco Targets Ther. 2017;10:1149–54.
37. Zhu J, Jia W, Wu C, Fu W, Xia H, Liu G, He J. Base excision repair gene polymorphisms and Wilms tumor susceptibility. EBioMedicine. 2018;33:88–93.
38. Zhu J, Fu W, Jia W, Xia H, Liu GC, He J. Association between NER pathway gene polymorphisms and Wilms tumor risk. Mol Ther Nucleic Acids. 2018;12:854–60.
39. Chen H, Duan F, Wang M, Zhu J, Zhang J, Cheng J, Li L, Li S, Li Y, Yang Z, et al. Polymorphisms in METTL3 gene and hepatoblastoma risk in Chinese children: A seven-center case-control study. Gene. 2021;800:145834.
40. Lin A, Hua RX, Zhou M, Fu W, Zhang J, Zhou H, Li S, Cheng J, Zhu J, Xia H, et al. YTHDC1 gene polymorphisms and Wilms tumor susceptibility in Chinese children: A five-center case-control study. Gene. 2021;783:145571.
41. Ma L, Hua RX, Lin H, Zhu J, Fu W, Lin A, Zhang J, Cheng J, Zhou H, Li S, et al. The contribution of WTAP gene variants to Wilms tumor susceptibility. Gene. 2020;754:144839.
42. Deng L, Hua R, Zhang Z, Zhu J, Zhang J, Cheng J, Li S, Zhou H, Liu G, He J, et al. METTL1 gene polymorphisms and Wilms tumor susceptibility in Chinese children: A five-center case-control study. Chin Med J (Engl). 2023;136(14):1750–2.
43. Deng L, Hua RX, Deng C, Zhu J, Zhang Z, Cheng J, Zhang J, Zhou H, Li S, Ruan J, et al. WDR4 gene polymorphisms and Wilms tumor susceptibility in Chinese children: A five-center case-control study. J Cancer. 2023;14(8):1293–300.
44. Liu H, Ling Y, Gong Y, Sun Y, Hou L, Zhang B. DNA damage induces N-acetyltransferase NAT10 gene expression through transcriptional activation. Mol Cell Biochem. 2007;300(1–2):249–58.
45. Zhang S, Liu Y, Ma X, Gao X, Ru Y, Hu X, Gu X. Recent advances in the potential role of RNA N4-acetylcytidine in cancer progression. Cell Commun Signal. 2024;22(1):49.
46. Zhang Y, Lei Y, Dong Y, Chen S, Sun S, Zhou F, Zhao Z, Chen B, Wei L, Chen J, et al. Emerging roles of RNA ac4C modification and NAT10 in mammalian development and human diseases. Pharmacol Ther. 2024;253:108576.

Publisher's note